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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,692	06/29/2001	Sudhir Agrawal	47508.556CN2	1859

23483 7590 06/28/2005

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/896,692	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-12,14,15 and 31-33* is/are allowed.

6)☒ Claim(s) *16-29,34-38,40 and 41* is/are rejected.

7)☒ Claim(s) *30 and 39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-15-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-18-05.

Claims 1-12 and 14-41 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 16-29, 34-38, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting HIV-1 or HIV-2 infection in an isolated cell in vitro, and for a method of exhibiting antiviral activity or treating HIV-1 or HIV-2 infection in a human comprising the intravenous administration of an oligonucleotide consisting of SEQ ID NO: 1, 2, 3, 4 or 5, does not reasonably provide enablement for methods of inhibiting HIV-1 or HIV-2 infection in cells in vivo comprising the administration of these antisense, or for methods of exhibiting antiviral activity or treating HIV-1 or HIV-2 infection in a mammal comprising the administration of an oligonucleotide comprising SEQ ID NO: 1, 2, 3, 4 or 5, nor for methods of introducing an intact oligonucleotide into a mammal comprising oral administration of unmodified antisense oligonucleotides, whereby the oligonucleotides are present in intact form in the systemic plasma following oral administration, for the reasons of record set forth in the Office action mailed 10-19-04.

Applicants' arguments filed 4-18-05 have been fully considered but they are not fully persuasive. Applicants argue that the full scope of the claims are enabled, which claims are drawn to methods of inhibiting HIV-1 or HIV-2 infection in vivo comprising the administration - via any route of administration and including oral administration - of SEQ ID NOS: 1, 2, 3, 4 or 5, which oligonucleotides comprise phosphorothioate internucleotide linkages. Applicants argue that the citations drawn upon to illustrate the general unpredictability of antisense delivery and efficacy are largely inapplicable to the instantly claimed invention. Applicants argue further that negative statements have been culled and selectively relied upon, essentially misconstruing the art of antisense treatment as it currently exists, and that citing isolated research failures n the antisense field in general cannot be said to support a lack of enablement. Applicants also assert, for instance, that ribozymes are more difficult to deliver in sufficient quantities to target cells than antisense because ribozymes are usually larger and have higher secondary structural constraints than antisense, thereby compromising their delivery. Applicants are correct that ribozymes are generally longer than antisense oligonucleotides and have secondary structures that perhaps impede their uptake by target cells compared to less structured antisense, but the general teachings addressing the use of antisense for disease treatment repeatedly warn the reader about the current unpredictability and pitfalls associated with antisense for treatments in vivo (albeit to a greater extent for larger molecules with higher order structure). Chirila et al (Biomaterials, Vol. 23, on page 321), in their abstract, set the tone regarding the unpredictability of antisense delivery in vivo: "[T]he adequate delivery of antisense oligondeoxynucleotides to

individual cells remains an important and inordinately difficult challenge." The difficulty of adequate delivery of antisense in vivo is reiterated throughout the article and, contrary to Applicants' assertions, is not an isolated comment or sentiment taken out of context (e.g. see last full paragraph of the introduction on p. 322: "The difficulty in finding an adequate delivery method for AS ODNs in relation to their cellular (or nuclear) uptake is currently perceived as one of the major drawbacks." See also p. 327, last full paragraph for additional challenges to delivering adequate quantities of antisense for achieving desired in vivo effects: "Many studies indicate that although ODNs can gain access to the target tissue in vivo, they are eliminated rapidly and repeated administration is required to achieve therapeutic effects." And, on p. 337, last paragraph, the final sentence of Chirila's conclusion unambiguously states the challenge currently facing antisense therapy: "As a new generation of drug therapy in an advanced stage of development, the antisense strategy only awaits a suitable delivery system in order to live up to its promise.").

And, contrary to Applicants' assertions, there is no size distinction recited for antisense in the instant claims, so the antisense embraced by the instant claims are not distinguishable in size from those described in the teachings of Peracchi et al, as implied in Applicants' response filed 4-18-05. The instant claims are rejected because the disclosure provides no teaching that the phosphorothioate containing (and otherwise unmodified) oligonucleotides are delivered to target cells in vivo following oral administration, and further whereby any viral infection is inhibited or treatment effects are provided. The intravenous administration and subsequent viral inhibition of the

claimed antisense are not necessarily correlative of the ability to orally administer phosphorothioated (and otherwise unmodified) oligonucleotides (See Agrawal et al, Molecular Med. Today, Vol. 6, on page 78, first full paragraph: "End-modified MBOs have shown improved specificity, biological activity, in vivo stability, pharmacokinetic and safety profiles over PS-oligonucleotides. Importantly, end-modified MBOs permit oral and colorectal administration of antisense oligonucleotides as a result of their increased in vivo metabolic stability."). Contrary to Applicants' assertions, these teachings of Agrawal concerning the incorporation of terminal modifications for increasing oral bioavailability of oligonucleotides have not been taken out of context or misconstrued, but are reasonably applied to the scope of enablement entitled to the instant claims.

Also consistent with the instant scope rejection is the scope of the allowed claim of USPN 5,591,721, cited by Applicants in their response on 4-18-05, which claim is drawn to a method for introducing an intact oligonucleoitde into a mammal comprising the oral administration of an oligonucleotide comprising phosphorothioate internucleotide linkages and further comprising at least two 2'-O-methyl-ribonucleotides at each terminus. With the terminal modifications claimed, the oligonucleoitde was found to be in intact form in systemic plasma at least six hours following oral administration. For these reasons, the scope of enablement rejection of record is maintained.

Allowable Subject Matter

Claims 1-12, 14, 15, 31-33 appear free of the prior art searched and of record. Claims 30 and 39 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ɔ 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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6-23-05